



(12) **United States Patent**
Pollard

(10) **Patent No.:** **US 9,511,083 B2**
(45) **Date of Patent:** **Dec. 6, 2016**

(54) **CARDIAC GLYCOSIDES TO TREAT CYSTIC FIBROSIS AND OTHER IL-8 DEPENDENT DISORDERS**

(71) Applicant: **Bette Pollard**, Potomac, MD (US)

(72) Inventor: **Bette Pollard**, Potomac, MD (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **14/040,392**

(22) Filed: **Sep. 27, 2013**

(65) **Prior Publication Data**

US 2014/0187505 A1 Jul. 3, 2014

Related U.S. Application Data

(63) Continuation of application No. 12/229,399, filed on Nov. 12, 2009, now Pat. No. 8,569,248, which is a continuation of application No. 10/515,260, filed as application No. PCT/US03/16733 on May 28, 2003.

(60) Provisional application No. 60/383,117, filed on May 28, 2002.

(51) **Int. Cl.**
A61K 31/704 (2006.01)
A61K 31/7048 (2006.01)

(52) **U.S. Cl.**
CPC **A61K 31/704** (2013.01); **A61K 31/7048** (2013.01)

(58) **Field of Classification Search**
USPC 514/26
See application file for complete search history.

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,545,623 A * 8/1996 Matsumori 514/26
6,380,167 B1 * 4/2002 Braude 514/26

FOREIGN PATENT DOCUMENTS

WO WO9728808 * 8/1997 A61K 31/705

OTHER PUBLICATIONS

Ammirante et al., "B-cell-derived lymphotoxin promotes castration-resistant prostate cancer." *Nature* 2010:464;302-306.*
Yeh et al., "Inhibitory effects of digitalis on the proliferation of adrogen dependent and independent prostate cancer cells." *The Journal of Urology*, vol. 166, pp. 1937-1942, Nov. 2001.*
Inoue et al., "Interleukin 8 Expression Regulates Tumorigenicity and Metastases in Androgen-independent Prostate Cancer." *Clinical Cancer Research*: vol. 6, pp. 2104-2119, May 2000.*
Ozen et al., "Widespread deregulation of microRNA expression in human prostate cancer." *Oncogene* (2008) 27, 1788-1793.*
Haustein et al., "Studies on cardioactive steroids IV Influence of nitrate ester on cardiac and extracardiac activity," *Pharmacology* 20:15-20, 1980.
Kulikov et al., "Ouabain activates signaling pathways associated with cell death in human neuroblastoma," 1768(7), pp. 1691 to 1702, *Biochim. Biophys. Acta*, Jul. 2007.
Qiu et al., "Proteomics investigation of protein expression changes in ouabain induced apoptosis in human umbilical vein endothelial cells," *J. Cell. Biochem.* 104(3), pp. 1054-1064, Jun. 1, 2008.
Qiu et al., "Comparative proteomics analysis reveals role of heat shock protein 60 in digoxin-induced toxicity in human endothelial cells," *Biochimica et Biophysica Acta* 1784 (2008) 1857-1864.
Yang et al., "Digitoxin induces apoptosis in cancer cells by inhibiting nuclear factor of activated T-cells-driven c-MYC expression," *Journal of Carcinogenesis* 12(8) 2013.

* cited by examiner

Primary Examiner — Walter Webb

(74) *Attorney, Agent, or Firm* — Walter Ottesen, P.A.

(57) **ABSTRACT**

Disclosed is the use of a cardiac glycoside to decrease or inhibit the secretion of proinflammatory mediators in the treatment of disease conditions characterized by elevated levels of the proinflammatory mediator. The cardiac glycoside is administered to a mammalian subject in need of such treatment, and dosage is adjusted to the mass of the recipient and the need of the recipient to reduce or inhibit the level of the proinflammatory mediator. The proinflammatory mediators suppressed by the invention include IL-8, IL-6, TNF α , ICAM-1, IFN γ , IL-1 β , MCP-1, MIP-2, and/or epithelial-mesenchymal-transition (EMT). The cardiac glycoside, digitoxin or oleandrin, can be formulated for administration by injection or as an aerosol administered to the respiratory tract or by being ingested, or as nose drops or nasal spray. According to one use, the digitoxin controls microRNA expression in castration-resistant prostate cancer. The microRNA suppresses IL-8 and IL-6 expression in these cells.

16 Claims, 11 Drawing Sheets